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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
REDDIG, PETER J	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/775,481	WALDMAN ET AL.
	Examiner	Art Unit
	PETER J. REDDIG	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04/18/2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *169,171,172 and 174-198* is/are pending in the application.

4a) Of the above claim(s) *188-198* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *169,171,172 and 174-187* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)	
1) ☒ Notice of References Cited (PTO-892)	4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐ Notice of Informal Patent Application
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.	6) ☐ Other: _____.

DETAILED ACTION

1. The Amendment filed April 18, 2011 in response to the Office Action of October 18, 2010 is acknowledged and has been entered. Previously pending claims 1-168, 170, and 173 have been cancelled, claims 169 and 171 have been amended and new claims 174-198 have been added.

Newly submitted claims 188-198 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims 188-198 comprise the step of administering to an individual an amount of an guanylyl cyclase C ligand that activates guanylyl cyclase C on cancer cells effective to increase the number of guanylyl cyclase C molecules on the surface of cancer cells treatment of individuals that have the cancers of claim 188, which is distinct from administering to said individual by substantially continuous infusion, a cytostatically effective amount of an ST receptor ligand per hour for a period of time sufficient to have a therapeutic effect by the cytotoxic effect of the ST receptor ligand, wherein ST receptor ligand molecules bind to ST receptors on the surface of a primary or metastasized colorectal, gastric or esophageal cancer cell in said individual and induces a cystostatic effect in said cells for inducing a cytostatic effect in cancer cells in the originally elected and examined claims. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 188-198 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 169, 171, 172, and 174-187 are currently being examined as drawn to the originally elected species.

Rejections Maintained

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 169, 171, 172, 174-187 remain or are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 5,879,656 (March, 1999, previously cited), in view of Shilubhai et al. (Cancer Research, Sep. 15, 2000 60:5151-5157, previously cited), and in view of Cohen (Int J Radiat Oncol Biol Phys, 1987, 13:251-8, previously cited), essentially for the reasons of record set forth below.

US Patent No. 5,879,656 teaches administering anti-guanylyl cyclase C antibodies, including monoclonal and chimeric, and GCC ligands in conjugated and unconjugated form with therapeutic agents to individuals for therapy of primary or metastasized colorectal cancer, see claims 30-31, col. 10-lines 33-45, col. 25-26, and col. 45-lines 1-10. US Patent No. 5,879,656 teaches that individuals suffering from primary and metastasized colorectal cancer can be readily identified and the compositions of the invention can be used to kill the cancer cells, see col. 7-lines 30-65. US Patent No. 5,879,656 teaches that the pharmaceutical compositions of the present invention may be administered either as individual therapeutic agents or in combination with other therapeutic agents. US Patent No. 5,879,656 teaches that the treatments of the present invention may be combined with conventional therapies, which may be administered sequentially or simultaneously. See col. 17-lines 25-33. US Patent No. 5,879,656 teaches using intravenous infusion of the compositions and that the dosage is varied depending several factors including pharmacodynamics, route of administration, and kind of concurrent treatment. See col. 17 and 18. US Patent No. 5,879,656 teaches multiple therapeutic agents such as 5-fluorouaracil and bleomycin, see the claims and col. 21-lines 35-65.

US Patent No. 5,879,656 teaches as set forth above, but does not teach the different doses, concentrations, and times of treatment claimed, humanized anti-guanylyl cyclase C monoclonal antibody or treating with calcium.

Shilubhai et al. teach that uroguanylin inhibits proliferation and induces apoptosis in colon adenocarcinoma cells and suppress colon polyp formation, see Abstract, Fig. 2-4 and Table 1.

Cohen teaches that to find the safest procedure for treating a tumor, one must search for that combination of factors which will maximize the conditional probability of controlling the tumor and avoiding injury in any normal tissues, this depends on several factors including dose, field-size, fractions, and time. See abstract.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of USPN 5,879,656 and use different doses and times of infusion of the unconjugated GCC ligands, such as uroguanylin, and antibodies comprising therapeutic agents, because Shilubhai teaches the anti-cancer activity of uroguanylin and Cohen teaches the best tumor treatment scheme is to maximize the chance of tumor control by optimizing factors such as dose and number of fractions and avoid complications. One would have been motivated to use different doses and times of infusion of the GCC ligands in order to optimize the dose needed to effectively treat the colorectal cancer and to avoid complications such as injury to normal tissue. It is noted that optimum suitable ranges may be obtained by routine experimentation, absent a showing of criticality or unexpected results.

It is noted that optimum suitable ranges may be obtained by routine experimentation, absent a showing of criticality or unexpected results. Additionally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See MPEP 2144.05(II).

Applicant argues that nothing in the combination of references discloses that activation of GCC renders cells more susceptible to radiation or cytotoxic agents. As discloses in the specification, GCC activation leads to elevated levels of cGMP which inhibit and slow the cell's progress through the cell cycle. Administering radiation or cytotoxic chemotherapy after activation of GCC has been completed renders the cells more sensitive to radiotherapy or cytotoxic chemotherapy. Nothing in the combined teachings in the art teach or suggest the invention as claimed.

Applicant argues that neither U.S. Patent No. 5,879,656 nor Shilubhai disclose that GCC activation renders cells more vulnerable to radiotherapy or cytotoxic chemotherapy administered after GCC activation. Nothing in Cohen, US Patent No. 6,251,439, Queen or Riechmann make up for this deficiency. Nothing in the combination of references teaches or suggests that pretreatment with a GCC activating compound will result in a more effective use of cytotoxic chemotherapy or radiation therapy by reducing the therapeutic index of the cytotoxic chemotherapy or radiation therapy.

Applicant argues that in addition, nothing in the combination of references teaches that Calcium increases the radiation and chemo-sensitivity which results after GCC activation. Applicants have shown that the role of calcium levels in inducing cell cycle arrest by GCC activation.

Applicant's arguments have been considered, but have not been found persuasive because the features upon which applicant relies (i.e., that activation of GCC renders cells more susceptible/vulnerable to radiation or cytotoxic agents, that pretreatment with a GCC activating compound will result in a more effective use of cytotoxic chemotherapy or radiation therapy by reducing the therapeutic index of the cytotoxic chemotherapy or radiation therapy or that calcium increases the radiation and chemo-sensitivity which results after GCC activation) to demonstrate a distinction between the claimed invention and cited are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Additionally, US Patent No. 5,879,656 teaches that ST/GCC ligands activates the

receptor upon binding. See col. 3-line 60 to col. 4-line 30 and col. 7-line 65 to col. 8-line 40. Thus, Applicant's arguments have not been found persuasive and the rejection is maintained.

Applicant argues that moreover, nothing in the combination of U.S. Patent No. 5,879,656, Shilubhai, Cohen, US Patent No. 6,251,439, Queen and Riechmann teach or suggest that activation of GCC leads to an increase in expression of GCC in cells which results in more targets on cell surfaces against which anti-GCC conjugates. The increase in GCC on the cell surface makes the use of anti-GCC moieties that are conjugated to cytotoxic moieties more effective since more conjugated GCC can be delivered to the cells thereby delivering more toxic substances. Accordingly, the methods of the claimed invention in which a conjugated cytotoxic anti-GCC agent is delivered following treatment with ligant that results in GCC activation are more effective than those in which a conjugated cytotoxic anti-GCC agent is delivered without prior GCC activation. GCC activation results in upregulation of GCC expression which results in more targets for conjugated cytotoxic anti-GCC agent to bind to and deliver their cytotoxic moiety.

Applicant's arguments have been considered, but have not been found persuasive because the claims drawn to an increase in expression of GCC are withdrawn and the examined claims are not so limited. Thus, Applicant's arguments have been considered, but have not been found persuasive.

3. Claims 169, 171, 172, 174-187 remain or are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 6,767,704 (Waldman March 27, 2000, previously cited), in view of Shilubhai et al. (Cancer Research, Sep. 15, 2000 60:5151-5157, previously cited), and

in further view of Cohen (Int J Radiat. Oncol. Biol. Phys, 1987, 13:251-8, previously cited) for the reasons of record set forth below.

US Patent No. 6,767,704 teaches administering conjugated and unconjugated GCC ligands and anti-guanylyl cyclase C humanized monoclonal antibodies with therapeutics to individuals for therapy of primary or metastasized colorectal, stomach or esophageal cancer, see claims col. 3-lines 50-55, col. 21-lines 55-60, col. 22-line 55 to col. 23-line 67, col. 29, 30 and col. 31-lines 63-67. US Patent No. 6,767,704 teaches that the compositions of the invention can be used to kill the cancer cells, see col. 21-lines 45-55. US Patent No. 6,767,704 teaches that the pharmaceutical compositions of the present invention may be administered either as individual therapeutic agents or in combination with other therapeutic agents. US Patent No. 6,767,704 teaches that the treatments of the present invention may be combined with conventional therapies, which may be administered sequentially or simultaneously. See col. 26-lines 4-11. US Patent No. 6,767,704 teaches using intravenous infusion of the compositions and that the dosage is varied depending several factors including pharmacodynamics, route of administration, and kind of concurrent treatment. See col. 26.. US Patent No. 6,767,704 teaches multiple therapeutic agents such as 5-fluorouaracil and bleomycin, see col. 22-line 55 to col. 23-line 67. Thus, given that US Patent No. 6,767,704 teaches administration of the antibodies and conventional chemotherapies, such as the described therapeutic agents, in combination sequentially or simultaneously, one of skill in the art would immediately envision administering the antibody and different therapeutic agents in the claimed order.

US Patent No. 6,767,704 teaches as set forth above, but does not teach the different doses, concentrations, and times of treatment claimed, or treating with calcium.

Shilubhai et al. teach that uroguanylin inhibits proliferation and induces apoptosis in colon adenocarcinoma cells and suppress colon polyp formation, see Abstract, Fig. 2-4 and Table 1.

Cohen teaches that to find the safest procedure for treating a tumor, one must search for that combination of factors which will maximize the conditional probability of controlling the tumor and avoiding injury in any normal tissues, this depends on several factors including dose, field-size, fractions, and time. See abstract.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of USPN 6,767,704 use different doses and times of infusion of the unconjugated GCC ligands, such as uroguanylin, and antibodies comprising therapeutic agents, because Shilubhai teaches the anti-cancer activity of uroguanylin and Cohen teaches the best tumor treatment scheme is to maximize the chance of tumor control by optimizing factors such as dose and number of fractions and avoid complications. One would have been motivated to use different doses and times of infusion of the GCC ligands in order to optimize the dose needed to effectively treat the colorectal cancer and to avoid complications such as injury to normal tissue. It is noted that optimum suitable ranges may be obtained by routine experimentation, absent a showing of criticality or unexpected results.

It is noted that optimum suitable ranges may be obtained by routine experimentation, absent a showing of criticality or unexpected results. Additionally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art

unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See MPEP 2144.05(II).

Applicants argue that nothing in the combination of references discloses that activation of GCC renders cells more susceptible to radiation or cytotoxic agents. As discloses in the specification, GCC activation leads to elevated levels of cGMP which inhibit and slow the cell's progress through the cell cycle. Administering radiation or cytotoxic chemotherapy after activation of GCC has been completed renders the cells more sensitive to radiotherapy or cytotoxic chemotherapy. Nothing in the combined teachings in the art teach or suggest the invention as claimed.

Applicant argues that neither U.S. Patent No. 6,767,704 nor Shilubhai disclose that GCC activation renders cells more vulnerable to radiotherapy or cytotoxic chemotherapy administered after GCC activation. Nothing in Cohen nor US Patent No. 6,251,439 make up for this deficiency. Nothing in the combination of references teaches or suggests that pretreatment with a GCC activating compound will result in a more effective use of cytotoxic chemotherapy or radiation therapy by reducing the therapeutic index of the cytotoxic chemotherapy or radiation therapy.

Applicant argues that in addition, nothing in the combination of references teaches that Calcium increases the radiation and chemo-sensitivity which results after GCC activation. Applicants have shown that the role of calcium levels in inducing cell cycle arrest by GCC activation.

Applicant's arguments have been considered, but have not been found persuasive because the features upon which applicant relies (i.e., that activation of GCC renders cells more susceptible/vulnerable to radiation or cytotoxic agents, that pretreatment with a GCC activating compound will result in a more effective use of cytotoxic chemotherapy or radiation therapy by reducing the therapeutic index of the cytotoxic chemotherapy or radiation therapy or that calcium increases the radiation and chemo-sensitivity which results after GCC activation) to demonstrate a distinction between the claimed invention and cited are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Additionally, Shilubhai et al. teaches that GCC ligands activate guanylyl cyclase C upon binding. See col. 3-abstrat. Thus, Applicant's arguments have not been found persuasive and the rejection is maintained.

Applicant argues that Moreover, nothing in the combination of U.S. Patent No. 5,879,656, Shilubhai, Cohen, nor US Patent No. 6,251,439, teach or suggest that activation of GCC leads to an increase in expression of GCC in cells which results in more targets on cell surfaces against which anti-GCC conjugates. The increase in GCC on the cell surface makes the use of anti-GCC moieties that are conjugated to cytotoxic moieties more effective since more conjugated GCC can be delivered to the cells thereby delivering more toxic substances. Accordingly, the methods of the claimed invention in which a conjugated cytotoxic anti-GCC agent is delivered following treatment with ligand that results in GCC activation are more effective than those in which a conjugated cytotoxic anti-GCC agent is delivered without prior GCC activation. GCC activation results in upregulation of GCC expression which results in more

targets for conjugated cytotoxic anti-GCC agent to bind to and deliver their cytotoxic moiety.

Applicant's arguments have been considered, but have not been found persuasive because the claims drawn to an increase in expression of GCC are withdrawn and the examined claims are not so limited. Thus, Applicant's arguments have been considered, but have not been found persuasive.

New Grounds of Rejection/Objection

Claim Objections

4. Claim 187 is objected to because of the following informalities: There is a duplicate comma on the fourth line of claim 187. Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 169, 171, 172, 174-187 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-58 of U.S. Patent No. 5,879,656 (Waldman March, 1999, previously cieted) in view of Shilubhai et al. (Cancer Research, Sep. 15, 2000 60:5151-5157, previously cited), and in view of Cohen (Int J Radiat. Oncol. Biol. Phys, 1987, 13:251-8, previously cited).

The claims of USPN 5,879,656 are drawn to a method of treating an individual suspected of suffering from metastasized colorectal cancer comprising the step of administering parenterally to said individual a pharmaceutical composition comprising a therapeutically effective amount of a conjugated compound comprising: a) a ST receptor binding moiety; and, b) an active moiety; wherein said active moiety is a radiostable active agent that is a radiostable therapeutic agent.

The claims of USPN 5,879,656 do not specifically teach administering an additional cytotoxic therapeutic agent or radiation, or the various times and doses of treatment claimed.

Shilubhai et al. teach that uroguanylin inhibits proliferation and induces apoptosis in colon adenocarcinoma cells and suppress colon polyp formation, see Abstract, Fig. 2-4 and Table 1.

Cohen teaches that to find the safest procedure for treating a tumor, one must search for that combination of factors which will maximize the conditional probability of controlling the tumor and avoiding injury in any normal tissues, this depends on several factors including dose, field-size, fractions, and time. See abstract.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use additionally cytotoxic therapeutic agents like 5-FU and bleomycin

because US Patent No. 5,879,656 teaches that the pharmaceutical compositions of the present invention may be administered either as individual therapeutic agents or in combination with other therapeutic agents and that the treatments of the present invention may be combined with conventional therapies, which may be administered sequentially or simultaneously like 5-FU and bleomycin. See col. 17-lines 25-33 and col. 21-lines 30-65. Thus, the administration of the additional cytotoxic therapeutic agents or radiation is within the scope of the treatment methods as claimed.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of USPN 5,879,656 and use different doses and times of administration of the GCC ligands and GCC antibodies comprising therapeutic agents, because Shilubhai teaches the anti-cancer activity of uroguanylin and Cohen teaches the best tumor treatment scheme is to maximize the chance of tumor control by optimizing factors such as dose and number of fractions and avoid complications. One would have been motivated to use different doses and times of infusion of the GCC ligands in order to optimize the dose needed to effectively treat the colorectal cancer and to avoid complications such as injury to normal tissue. It is noted that optimum suitable ranges may be obtained by routine experimentation, absent a showing of criticality or unexpected results. Additionally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See MPEP 2144.05(II).

6. Claims 169, 171, 172, 174-187 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10-13 of U.S. Patent No. 5,962,220 (Waldman Oct. 1999, IDS) in view of U.S. Patent No. 5,879,656 (Waldman March, 1999), in view of Shilubhai et al. (Cancer Research, Sep. 15, 2000 60:5151-5157, previously cited), and in view of Cohen (Int J Radiat. Oncol. Biol. Phys, 1987, 13:251-8, previously cited).

The claims of USPN 5,962,220 are drawn to a method of treating an individual suspected of suffering from colorectal cancer comprising the steps of administering to said individual a therapeutically effective amount of a pharmaceutical composition comprising: a) a pharmaceutically acceptable carrier or diluent, and, b) a conjugated compound comprising: i) an ST receptor binding moiety; and, ii) an active moiety; wherein said ST receptor binding moiety is selected from the group consisting of: SEQ ID NO:2, SEQ ID NO:3, SEQ ID NOS:5-54 and an amino acid sequence identical to a contiguous amino acid portion of SEQ ID NO:2, SEQ ID NO:3, SEQ ID NOS:5-54 which is capable of binding to an ST receptor protein, and said active moiety is an antisense molecule that inhibits or prevents transcription or translation of colorectal cancer-associated genes.

The claims of USPN 5,962,220 do not specifically teach administering an additional cytotoxic therapeutic agent or radiation, or the various times and doses of treatment claimed.

US Patent No. 5,879,656 teaches administering anti-guanylyl cyclase C antibody ligands and GCC peptide ligands in conjugated and unconjugated form with therapeutic agents to individuals for therapy of primary or metastasized colorectal cancer, see claims 30-31, col. 10-lines 33-45, col. 25-26, and col. 45-lines 1-10. US Patent No. 5,879,656 teaches that individuals

suffering from primary and metastasized colorectal cancer can be readily identified and the compositions of the invention can be used to kill the cancer cells, see col. 7-lines 30-65. US Patent No. 5,879,656 teaches that the pharmaceutical compositions of the present invention may be administered either as individual therapeutic agents or in combination with other therapeutic agents. US Patent No. 5,879,656 teaches that the treatments of the present invention may be combined with conventional therapies, which may be administered sequentially or simultaneously. See col. 17-lines 25-33. US Patent No. 5,879,656 teaches using intravenous infusion of the compositions and that the dosage is varied depending several factors including pharmacodynamics, route of administration, and kind of concurrent treatment. See col. 17 and 18. US Patent No. 5,879,656 teaches multiple therapeutic agents such as 5-fluorouaracil and bleomycin, see the claims and col. 21-lines 35-65.

Shilubhai et al. teach that uroguanylin inhibits proliferation and induces apoptosis in colon adenocarcinoma cells and suppress colon polyp formation, see Abstract, Fig. 2-4 and Table 1.

Cohen teaches that to find the safest procedure for treating a tumor, one must search for that combination of factors which will maximize the conditional probability of controlling the tumor and avoiding injury in any normal tissues, this depends on several factors including dose, field-size, fractions, and time. See abstract.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use additional cytotoxic therapeutic agents like 5-FU and bleomycin because US Patent No. 5,879,656 teaches the GCC ligands invention may be administered either as individual therapeutic agents or in combination with other therapeutic agents and that the

treatments of the present invention may be combined with conventional therapies, which may be administered sequentially or simultaneously like 5-FU and bleomycin. See col. 17-lines 25-33 and col. 21-lines 30-65. Thus, the administration of the additional cytotoxic therapeutic agents or radiation would have been obvious as combination therapy for colorectal, primary or metastasized, cancer is routinely performed in the art as taught by USPN 5,879,656.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of USPN 5,962,220 and use different doses and times of administration of the GCC ligands and GCC antibodies comprising therapeutic agents, because Shilubhai teaches the anti-cancer activity of uroguanylin and Cohen teaches the best tumor treatment scheme is to maximize the chance of tumor control by optimizing factors such as dose and number of fractions and avoid complications. One would have been motivated to use different doses and times administration of the GCC ligands in order to optimize the dose needed to effectively treat the colorectal cancer and to avoid complications such as injury to normal tissue. It is noted that optimum suitable ranges may be obtained by routine experimentation, absent a showing of criticality or unexpected results. Additionally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See MPEP 2144.05(II).

7. Claims 169, 171, 172, 174-187 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 6-8 of U.S. Patent No. 6,060,037 (Waldman, May 2000, IDS), in view of U.S. Patent No. 5,879,656 (Waldman March, 1999), in view of Shilubhai et al. (Cancer Research, Sep. 15, 2000 60:5151-5157, previously cited), and in view of Cohen (Int J Radiat. Oncol. Biol. Phys, 1987, 13:251-8, previously cited).

The claims of USPN 6,060,037 are drawn to a method of treating an individual suspected of suffering from metastasized colorectal cancer comprising the step of administering parenterally to said individual a therapeutically effective amount of a sterile pharmaceutical composition that comprises a) a pharmaceutically acceptable carrier or diluent, and, b) a conjugated compound which comprises i) a ST receptor binding moiety; and, ii) an active moiety that is a therapeutic agent that causes cell death; wherein said conjugated compound binds to an ST receptor on a metastasized colorectal tumor cell and said active moiety causes the death of said cell.

The claims of USPN 6,060,037 do not specifically teach administering an additional cytotoxic therapeutic agent or radiation, or the various times and doses of treatment claimed.

US Patent No. 5,879,656 teaches administering anti-guanylyl cyclase C antibody ligands and GCC peptide ligands in conjugated and unconjugated form with therapeutic agents to individuals for therapy of primary or metastasized colorectal cancer, see claims 30-31, col. 10-lines 33-45, col. 25-26, and col. 45-lines 1-10. US Patent No. 5,879,656 teaches that individuals suffering from primary and metastasized colorectal cancer can be readily identified and the compositions of the invention can be used to kill the cancer cells, see col. 7-lines 30-65. US Patent No. 5,879,656 teaches that the pharmaceutical compositions of the present invention may

be administered either as individual therapeutic agents or in combination with other therapeutic agents. US Patent No. 5,879,656 teaches that the treatments of the present invention may be combined with conventional therapies, which may be administered sequentially or simultaneously. See col. 17-lines 25-33. US Patent No. 5,879,656 teaches using intravenous infusion of the compositions and that the dosage is varied depending several factors including pharmacodynamics, route of administration, and kind of concurrent treatment. See col. 17 and 18. US Patent No. 5,879,656 teaches multiple therapeutic agents such as 5-fluorouaracil and bleomycin, see the claims and col. 21-lines 35-65.

Shilubhai et al. teach that uroguanylin inhibits proliferation and induces apoptosis in colon adenocarcinoma cells and suppress colon polyp formation, see Abstract, Fig. 2-4 and Table 1.

Cohen teaches that to find the safest procedure for treating a tumor, one must search for that combination of factors which will maximize the conditional probability of controlling the tumor and avoiding injury in any normal tissues, this depends on several factors including dose, field-size, fractions, and time. See abstract.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use additional cytotoxic therapeutic agents like 5-FU and bleomycin because US Patent No. 5,879,656 teaches the GCC ligands invention may be administered either as individual therapeutic agents or in combination with other therapeutic agents and that the treatments of the present invention may be combined with conventional therapies, which may be administered sequentially or simultaneously like 5-FU and bleomycin. See col. 17-lines 25-33 and col. 21-lines 30-65. Thus, the administration of the additional cytotoxic therapeutic agents

or radiation would have been obvious as combination therapy for colorecatl cancer, primary or metastasized, is routinely performed in the art as taught by USPN 5,879,656.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of USPN 6,060,037 and use different doses and times of administration of the GCC ligands and GCC antibodies comprising therapeutic agents, because Shilubhai teaches the anti-cancer activity of uroguanylin and Cohen teaches the best tumor treatment scheme is to maximize the chance of tumor control by optimizing factors such as dose and number of fractions and avoid complications. One would have been motivated to use different doses and times of administration of the GCC ligands in order to optimize the dose needed to effectively treat the colorectal cancer and to avoid complications such as injury to normal tissue. It is noted that optimum suitable ranges may be obtained by routine experimentation, absent a showing of criticality or unexpected results. Additionally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See MPEP 2144.05(II).

8. Claims 169, 171, 172, 174-187 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 14-17 of U.S. Patent No. 6,087,109 (Waldman, July 2000, IDS), in view of U.S. Patent No. 5,879,656 (Waldman March,

1999), in view of Shilubhai et al. (Cancer Research, Sep. 15, 2000 60:5151-5157, previously cited), and in view of Cohen (Int J Radiat. Oncol. Biol. Phys, 1987, 13:251-8, previously cited).

The claims of USPN 6,060,037 are drawn a method of treating an individual suspected of suffering from colorectal cancer comprising the steps of administering to said individual a therapeutically effective amount of a pharmaceutical composition according to claim 7.

The claims of USPN 6,087,109 do not specifically teach administering an additional cytotoxic therapeutic agent or radiation, or the various times and doses of treatment claimed.

US Patent No. 5,879,656 teaches administering anti-guanylyl cyclase C antibody ligands and GCC peptide ligands in conjugated and unconjugated form with therapeutic agents to individuals for therapy of primary or metastasized colorectal cancer, see claims 30-31, col. 10-lines 33-45, col. 25-26, and col. 45-lines 1-10. US Patent No. 5,879,656 teaches that individuals suffering from primary and metastasized colorectal cancer can be readily identified and the compositions of the invention can be used to kill the cancer cells, see col. 7-lines 30-65. US Patent No. 5,879,656 teaches that the pharmaceutical compositions of the present invention may be administered either as individual therapeutic agents or in combination with other therapeutic agents. US Patent No. 5,879,656 teaches that the treatments of the present invention may be combined with conventional therapies, which may be administered sequentially or simultaneously. See col. 17-lines 25-33. US Patent No. 5,879,656 teaches using intravenous infusion of the compositions and that the dosage is varied depending several factors including pharmacodynamics, route of administration, and kind of concurrent treatment. See col. 17 and 18. US Patent No. 5,879,656 teaches multiple therapeutic agents such as 5-fluorouaracil and bleomycin, see the claims and col. 21-lines 35-65.

Shilubhai et al. teach that uroguanylin inhibits proliferation and induces apoptosis in colon adenocarcinoma cells and suppress colon polyp formation, see Abstract, Fig. 2-4 and Table 1.

Cohen teaches that to find the safest procedure for treating a tumor, one must search for that combination of factors which will maximize the conditional probability of controlling the tumor and avoiding injury in any normal tissues, this depends on several factors including dose, field-size, fractions, and time. See abstract.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use additional cytotoxic therapeutic agents like 5-FU and bleomycin because US Patent No. 5,879,656 teaches the GCC ligands invention may be administered either as individual therapeutic agents or in combination with other therapeutic agents and that the treatments of the present invention may be combined with conventional therapies, which may be administered sequentially or simultaneously like 5-FU and bleomycin. See col. 17-lines 25-33 and col. 21-lines 30-65. Thus, the administration of the additional cytotoxic therapeutic agents or radiation would have been obvious as combination therapy for colorectal cancer, primary or metastasized, is routinely performed in the art as taught by USPN 5,879,656.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of USPN 6,087,109 and use different doses and times of administration of the GCC ligands, because Shilubhai teaches the anti-cancer activity of uroguanylin and Cohen teaches the best tumor treatment scheme is to maximize the chance of tumor control by optimizing factors such as dose and number of fractions and avoid complications. One would have been motivated to use different doses and times of

administration of the GCC ligands in order to optimize the dose needed to effectively treat the colorectal cancer and to avoid complications such as injury to normal tissue. It is noted that optimum suitable ranges may be obtained by routine experimentation, absent a showing of criticality or unexpected results. Additionally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See MPEP 2144.05(II).

9. Claims 169, 171, 172, 174-187 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-46 of U.S. Patent No. 7,744,870 (Waldman, June 2010), in view of U.S. Patent No. 5,879,656 (Waldman March, 1999), in view of Shilubhai et al. (Cancer Research, Sep. 15, 2000 60:5151-5157, previously cited), and in view of Cohen (Int J Radiat. Oncol. Biol. Phys, 1987, 13:251-8, previously cited).

The claims of USPN 7,744,870 are drawn to a method of treating an individual suspected of suffering from metastatic colorectal cancer comprising the step of administering to said individual a pharmaceutical composition that comprises: a) a heat stable enterotoxin (ST) receptor ligand in combination with; b) an active agent in an amount effective to cause a cytotoxic or cytostatic effect on metastasized colorectal cancer cells without causing lethal side effects on the individual, wherein the active agent causes cell death, inhibits cell division or

induces differentiation; and c) a pharmaceutically acceptable carrier or diluent wherein said ST receptor ligand is an antibody, Fab or $F(AB)_2$.

The claims of USPN 7,744,870 do not specifically teach administering an additional cytotoxic therapeutic agent or radiation, or the various times and doses of treatment claimed.

US Patent No. 5,879,656 teaches administering anti-guanylyl cyclase C antibody ligands and GCC peptide ligands in conjugated and unconjugated form with therapeutic agents to individuals for therapy of primary or metastasized colorectal cancer, see claims 30-31, col. 10-lines 33-45, col. 25-26, and col. 45-lines 1-10. US Patent No. 5,879,656 teaches that individuals suffering from primary and metastasized colorectal cancer can be readily identified and the compositions of the invention can be used to kill the cancer cells, see col. 7-lines 30-65. US Patent No. 5,879,656 teaches that the pharmaceutical compositions of the present invention may be administered either as individual therapeutic agents or in combination with other therapeutic agents. US Patent No. 5,879,656 teaches that the treatments of the present invention may be combined with conventional therapies, which may be administered sequentially or simultaneously. See col. 17-lines 25-33. US Patent No. 5,879,656 teaches using intravenous infusion of the compositions and that the dosage is varied depending several factors including pharmacodynamics, route of administration, and kind of concurrent treatment. See col. 17 and 18. US Patent No. 5,879,656 teaches multiple therapeutic agents such as 5-fluorouaracil and bleomycin, see the claims and col. 21-lines 35-65.

Shilubhai et al. teach that uroguanylin inhibits proliferation and induces apoptosis in colon adenocarcinoma cells and suppress colon polyp formation, see Abstract, Fig. 2-4 and Table 1.

Cohen teaches that to find the safest procedure for treating a tumor, one must search for that combination of factors which will maximize the conditional probability of controlling the tumor and avoiding injury in any normal tissues, this depends on several factors including dose, field-size, fractions, and time. See abstract.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use additional cytotoxic therapeutic agents like 5-FU and bleomycin because US Patent No. 5,879,656 teaches the GCC ligands invention may be administered either as individual therapeutic agents or in combination with other therapeutic agents and that the treatments of the present invention may be combined with conventional therapies, which may be administered sequentially or simultaneously like 5-FU and bleomycin. See col. 17-lines 25-33 and col. 21-lines 30-65. Thus, the administration of the additional cytotoxic therapeutic agents or radiation would have been obvious as combination therapy for colorectal cancer, primary or metastasized, is routinely performed in the art as taught by USPN 5,879,656.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of USPN 7,744,870 and use different doses and times of administration of the GCC ligands, because Shilubhai teaches the anti-cancer activity of uroguanylin and Cohen teaches the best tumor treatment scheme is to maximize the chance of tumor control by optimizing factors such as dose and number of fractions and avoid complications. One would have been motivated to use different doses and times of administration of the GCC ligands in order to optimize the dose needed to effectively treat the colorectal cancer and to avoid complications such as injury to normal tissue. It is noted that optimum suitable ranges may be obtained by routine experimentation, absent a showing of

criticality or unexpected results. Additionally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See MPEP 2144.05(II).

10. Claims 169, 171, 172, 174-187 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-46 of U.S. Patent No. 7,854,933 (Waldman et al., Dec. 2010), in view of U.S. Patent No. 5,879,656 (Waldman March, 1999), in view of Shilubhai et al. (Cancer Research, Sep. 15, 2000 60:5151-5157, previously cited), and in view of Cohen (Int J Radiat. Oncol. Biol. Phys, 1987, 13:251-8, previously cited).

The claims of USPN 7,854,933 are drawn to a method of treating an individual suspected of suffering from primary and/or metastatic esophageal cancer comprising the steps of administering to said individual a therapeutically effective amount of a composition comprising: i) a guanylyl cyclase C ligand; and ii) a therapeutic agent, wherein the guanylyl cyclase C ligand is conjugated to the therapeutic agent, and wherein the guanylyl cyclase C ligand is an antibody which binds to SEQ ID NO: 2.

The claims of USPN 7,854,933 do not specifically teach administering an additional cytotoxic therapeutic agent or radiation, or the various times and doses of treatment claimed.

US Patent No. 5,879,656 teaches administering anti-guanylyl cyclase C antibody ligands and GCC peptide ligands in conjugated and unconjugated form with therapeutic agents to individuals for therapy of primary or metastasized colorectal cancer, see claims 30-31, col. 10-

lines 33-45, col. 25-26, and col. 45-lines 1-10. US Patent No. 5,879,656 teaches that individuals suffering from primary and metastasized colorectal cancer can be readily identified and the compositions of the invention can be used to kill the cancer cells, see col. 7-lines 30-65. US Patent No. 5,879,656 teaches that the pharmaceutical compositions of the present invention may be administered either as individual therapeutic agents or in combination with other therapeutic agents. US Patent No. 5,879,656 teaches that the treatments of the present invention may be combined with conventional therapies, which may be administered sequentially or simultaneously. See col. 17-lines 25-33. US Patent No. 5,879,656 teaches using intravenous infusion of the compositions and that the dosage is varied depending several factors including pharmacodynamics, route of administration, and kind of concurrent treatment. See col. 17 and 18. US Patent No. 5,879,656 teaches multiple therapeutic agents such as 5-fluorouaracil and bleomycin, see the claims and col. 21-lines 35-65.

Shilubhai et al. teach that uroguanylin inhibits proliferation and induces apoptosis in colon adenocarcinoma cells and suppress colon polyp formation, see Abstract, Fig. 2-4 and Table 1.

Cohen teaches that to find the safest procedure for treating a tumor, one must search for that combination of factors which will maximize the conditional probability of controlling the tumor and avoiding injury in any normal tissues, this depends on several factors including dose, field-size, fractions, and time. See abstract.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use additional cytotoxic therapeutic agents like 5-FU and bleomycin because US Patent No. 5,879,656 teaches the GCC ligands invention may be administered either

as individual therapeutic agents or in combination with other therapeutic agents and that the treatments of the present invention may be combined with conventional therapies, which may be administered sequentially or simultaneously like 5-FU and bleomycin. See col. 17-lines 25-33 and col. 21-lines 30-65. Thus, the administration of the additional cytotoxic therapeutic agents or radiation would have been obvious as combination therapy for esophageal cancer, primary or metastasized, is routinely performed in the art as taught by USPN 5,879,656.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of USPN 7,854,933 and use different doses and times of administration of the GCC ligands, because Shilubhai teaches the anti-cancer activity of uroguanylin and Cohen teaches the best tumor treatment scheme is to maximize the chance of tumor control by optimizing factors such as dose and number of fractions and avoid complications. One would have been motivated to use different doses and times of administration of the GCC ligands in order to optimize the dose needed to effectively treat the colorectal cancer and to avoid complications such as injury to normal tissue. It is noted that optimum suitable ranges may be obtained by routine experimentation, absent a showing of criticality or unexpected results. Additionally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See MPEP 2144.05(II).

11. Claims 169, 171, 172, 174-187 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 21 of co-pending application 11/494,901, in view of U.S. Patent No. 5,879,656 (Waldman March, 1999), in view of Shilubhai et al. (Cancer Research, Sep. 15, 2000 60:5151-5157, previously cited), and in view of Cohen (Int J Radiat. Oncol. Biol. Phys, 1987, 13:251-8, previously cited).

Claim 21 of the '901 application is drawn to a method of treating an individual suspectedof suffering from metastasized colorectal cancer comprising the steps of administering to said individual a pharmaceutical composition of claim 12, wherein said active moiety is a radioactive agent and said conjugated compound is present in a therapeutically in humans suffering from colorectal cancerThe claims of USPN 7,744,870 do not specifically teach administering an additional cytotoxic therapeutic agent or radiation, or the various times and doses of treatment claimed.

US Patent No. 5,879,656 teaches administering anti-guanylyl cyclase C antibody ligands and GCC peptide ligands in conjugated and unconjugated form with therapeutic agents to individuals for therapy of primary or metastasized colorectal cancer, see claims 30-31, col. 10-lines 33-45, col. 25-26, and col. 45-lines 1-10. US Patent No. 5,879,656 teaches that individuals suffering from primary and metastasized colorectal cancer can be readily identified and the compositions of the invention can be used to kill the cancer cells, see col. 7-lines 30-65. US Patent No. 5,879,656 teaches that the pharmaceutical compositions of the present invention may be administered either as individual therapeutic agents or in combination with other therapeutic agents. US Patent No. 5,879,656 teaches that the treatments of the present invention may be combined with conventional therapies, which may be administered sequentially or

simultaneously. See col. 17-lines 25-33. US Patent No. 5,879,656 teaches using intravenous infusion of the compositions and that the dosage is varied depending several factors including pharmacodynamics, route of administration, and kind of concurrent treatment. See col. 17 and 18. US Patent No. 5,879,656 teaches multiple therapeutic agents such as 5-fluorouaracil and bleomycin, see the claims and col. 21-lines 35-65.

Shilubhai et al. teach that uroguanylin inhibits proliferation and induces apoptosis in colon adenocarcinoma cells and suppress colon polyp formation, see Abstract, Fig. 2-4 and Table 1.

Cohen teaches that to find the safest procedure for treating a tumor, one must search for that combination of factors which will maximize the conditional probability of controlling the tumor and avoiding injury in any normal tissues, this depends on several factors including dose, field-size, fractions, and time. See abstract.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use additional cytotoxic therapeutic agents like 5-FU and bleomycin because US Patent No. 5,879,656 teaches the GCC ligands invention may be administered either as individual therapeutic agents or in combination with other therapeutic agents and that the treatments of the present invention may be combined with conventional therapies, which may be administered sequentially or simultaneously like 5-FU and bleomycin. See col. 17-lines 25-33 and col. 21-lines 30-65. Thus, the administration of the additional cytotoxic therapeutic agents or radiation would have been obvious as combination therapy for colorectal cancer, primary or metastasized, is routinely performed in the art as taught by USPN 5,879,656.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of claim 21 of the '901 application and use different doses and times of administration of the GCC ligands, because Shilubhai teaches the anti-cancer activity of uroguanylin and Cohen teaches the best tumor treatment scheme is to maximize the chance of tumor control by optimizing factors such as dose and number of fractions and avoid complications. One would have been motivated to use different doses and times of administration of the GCC ligands in order to optimize the dose needed to effectively treat the colorectal cancer and to avoid complications such as injury to normal tissue. It is noted that optimum suitable ranges may be obtained by routine experimentation, absent a showing of criticality or unexpected results. Additionally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See MPEP 2144.05(II).

12. No claims allowed.

13. Applicant's amendment necessitated the new grounds of rejections. Thus, **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Misook Yu can be reached on (571) 272-0839. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Peter J Reddig/
Primary Examiner, Art Unit 1642